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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/870,902	05/31/2001	Jonathan Robert Lamb		7755

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EXAMINER	
EWOLDT, GERALD R	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 06/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/870,902	LAMB ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,4,5,8-13,17,19,20,25,30 and 32* is/are pending in the application.

4a) Of the above claim(s) *10-13,17,30 and 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *2,4,5,8,9,19,20 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and remarks, filed 4/04/05, are acknowledged. In view of the amendment, the previous rejections under the second paragraph of 35 U.S.C. 112 have been withdrawn. Additionally, the previous rejections under 35 U.S.C. 102 and 103(a) of Claims 2, 4, 5, 8, 9 have been withdrawn in view of Applicant's argument that the prior art teaches that mature dendritic cells (DCs) would not function in the method of the instant claims.

2. Claims 10-13, 17, 30, and 32 stand withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 2, 4, 5, 8, 9, 19, 20, and 25 read on the elected invention and are being acted upon.

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 19 and 25 stand rejected under 35 U.S.C. 102(b) as being clearly anticipated by Steinbrink et al. (1997).

As set forth previously, Steinbrink et al. teaches a method for producing a tolerogenic regulatory lymphocyte comprising incubating a dendritic cell (DC) with the immunosuppressive cytokine IL-10 and antigen (HA) and contacting said DC with a lymphocyte to produce a tolerogenic regulatory lymphocyte (see Materials and Methods and Figure 7). Note that the claims also recite incubating the DC with a composition capable of "upgrading" the expression of Notch or the Notch ligand Delta (the elected species) however, this "upgrading" is inherent to the method of the reference. The specification, in effect, merely further characterizes the mechanism by which a known method produces a tolerogenic regulatory lymphocyte.

Applicant has not addressed this rejection because the claims have not been amended as set forth in the remarks.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claim 20 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Steinbrink et al. (1997) in view of Scholz et al. (1998).

As set forth previously, Steinbrink et al. has been discussed above.

The reference teaching differs from the claimed invention only in that it does not teach the myelin basic protein (MBP) antigen.

Scholz et al. teaches that MBP is an important autoantigen in multiple sclerosis (MS) (see particularly page 1532, column 2). The reference further teaches that activated MBP-specific CD4 T cells play a role in the pathogenesis of MS (see particularly page 1538, column 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention to perform a method for producing a regulatory tolerogenic lymphocyte comprising incubating a DC with the immunosuppressive cytokine IL-10 and antigen and contacting said DC with a lymphocyte to produce a tolerogenic regulatory lymphocyte, as taught by Steinbrink et al., employing MBP as the antigen. One of ordinary skill in the art at the time the invention was made would have been motivated to employ MBP as the antigen given the teachings of Scholz et al. that MBP is an important autoantigen in MS and that activated MBP-specific CD4 T cells play a role in the pathogenesis of MS. Thus, a tolerogenic lymphocyte capable of regulating autoreactive MBP-specific CD4 T cells would comprise a valuable tool for the study and possible treatment of MS.

Again, Applicant has not addressed this rejection because the claim has not been amended as set forth in the remarks.

7. The following are new grounds of rejection necessitated by Applicant's amendment.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 2, 4, 5, 8, 9, 19, 20, and 25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the specification provides insufficient evidence that the method for producing a regulatory lymphocyte would function as claimed.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, see *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. With these teachings in mind, an enabling disclosure, commensurate in scope with the breadth of the claimed invention, is required.

The claimed method presumably functions as follows. An APC, e.g., a DC, is contacted with a composition, e.g., IL-10, which upregulates Notch, or a Notch ligand, e.g., Serrate or Delta, which somehow causes the APC to become a regulatory APC that, upon contact with a lymphocyte, e.g., a T cell, causes the

lymphocyte to become a regulatory lymphocyte. While less important terms are defined in the specification, curiously, "regulatory lymphocyte" is not. In the instant context, however, a "regulatory lymphocyte" is considered to be a tolerogenic or tolerance inducing lymphocyte (see, for example, pages 1 and 14).

A review of the instant specification discloses no relevant examples nor data in support of the claimed invention. Examples 1-5 comprise a collection of experiments which are either irrelevant, prophetic, absent any results, or a combination of the above. Example 8 discloses that PCR analysis shows that Notch 1 is downregulated in CD4+ T cells upon incubation with IL-10. Additionally, IL-10 has no effect on Serrate 1 or Delta 1 expression. While basically irrelevant to the claimed method, the Example does show that IL-10 does not induce Notch ligands in all leukocytes, and can even downregulate Notch in some cell types. Example 9 discloses that PCR analysis shows that Serrate 1 is upregulated in an undisclosed type of spleen-derived CD11c+ DC upon incubation with IL-10, but that Notch 2 is unchanged. Example 10 discloses that PCR analysis shows that Delta 1, Notch 2, and Notch 4 are upregulated in a naïve B cell upon incubation with IL-10, but that Serrate 1 is unchanged. The most relevant example to the claimed method, Example 11, discloses that PCR analysis shows that Serrate 1 is upregulated, but Delta 1 is downregulated, in bone marrow-derived CD11c+ mature DC upon incubation with IL-10. In combination these results show that IL-10 has different effects on different cell types, or even the same cell types (DCs) from different sources, thus, generalizations about the effect of cell culture in IL-10 cannot be made based on these findings. Accordingly, these disclosures cannot support the broadly claimed method, employing: A) *any* type of lymphocyte, B) *any* type of mature APC, and C) *any* type of Notch or Notch ligand upregulator.

More importantly note that the previous examples merely disclose the unpredictability of upregulating Notch or a Notch ligand. The much more complex issue of actually producing a regulatory lymphocyte is not addressed at all. Thus, a review of the state of the art is in order. Morel et al. (1997) teaches that IL-10 culture decreases DCs' capacity to induce T cells, but it does not eliminate it (Figure 8), nor does it cause IL-10 treated DCs to induce regulatory or tolerogenic T cells. Beissert et al. (1995) teaches that IL-10 treatment has no effect on mature DCs (Discussion). And as argued by

Applicant in the instant remarks, Steinbrink et al. (1997) teaches that IL-10 has no effect on fully mature DCs.

Given Applicant's failure to address these contradictions, it is the Examiner's position that the method encompassed by the instant claims is not enabled by the instant specification.

10. Claims 2, 4, 5, 8, 9 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically, a method employing a "mature antigen presenting cell" as recited in Claim 1.

Applicant indicates that support for the new amendment can be found throughout the specification and original claims, however, no support for the limitation has been found.

11. No claim is allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

14. **Please Note**: Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

6/23/05

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Primary Examiner
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